Leadership Opportunities in the Emerging Field of Translational Science: Forging a Path for Biomarkers from Academic Discovery to Clinical Laboratory Use

By

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Abstract

Translational science is focused on improving human health by bringing scientific discoveries from the academic research laboratory (bench) into clinical practice (bedside). In September 2004, the National Institutes of Health established a roadmap for medical research to overcome major hurdles of moving technologies from bench to bedside. Since then there have been great successes in the areas of therapeutics, medical devices and community interventions. However, translation of biomarkers from discovery to the clinical laboratory has remained sluggish. Rapid translation calls for a more defined path from academic discovery to clinical use. Leadership opportunities in academia and industry abound as this path is forged in the clinical diagnostic arena.

Rapid translation of laboratory diagnostics is vital to patient care. Clinical laboratory diagnostics are primary tools used by clinicians to make decisions impacting patient care. Proteomic and genomic discoveries in the academic arena are vast yet rarely move into clinical validation and transfer to industry due to intellectual property disputes, scarce funding resources for validation, method development expertise and lack of communication between academia and industry. The objective of this paper is to define the barriers that exist for a biomarker along the path to a widely adopted assay in the clinical laboratory, offer solutions and define potential leadership opportunities in this emerging field.

Barriers to translation of biomarkers from discovery to clinical use continue to persist. There may be limited communication between academic researchers and clinical laboratory leaders. Methods used to discover useful biomarkers may not be suitable for clinical laboratory high-volume testing. Often, development, method and clinical validation of the biomarker are necessary before an industry partner is interested in investing in the high-risk/high-return discovery as a potential clinical diagnostic assay. It has been challenging to secure funding for prospective clinical validation of diagnostic assays in the academic setting. Additionally, there is a gap in training and personnel at the academic level to take a biomarker beyond the discovery phase. The expertise to develop methods utilized in clinical laboratories lies in the hands of industry research and development experts cautious to invest in early method development of a

biomarker without evidence of its performance in the target population. Thus, many biomarkers never make it out of the discovery phase.

A review of current literature reveals great opportunities exist for collaboration between clinical laboratories, academic researchers and industry leaders to move biomarkers rapidly from bench to bedside. During review of the literature and my own experience translating biomarkers for clinical use, it was discovered that no curriculum exist academia to train future scientists for method development on platforms suitable for clinical laboratory use. Just as communication has improved between basic science researchers and clinicians to facilitate translation of therapeutics into practice, so must the clinical laboratory, diagnostic industry and academia collaborate to form a clear path to translate biomarkers into useful clinical tools. Barriers and solutions to translation of biomarkers are discussed and recommendations provided for forging a clear path for biomarkers using the existing NIH Clinical and Translational Science infrastructure across college campuses in the United States as well as the Early Detection Research Network and the Biomarker Consortium resources.

By rapidly delivering efficacious and effective diagnostic tools to clinicians, the implications for public health are many. Sensitive diagnostic laboratory assays may prevent costly treatment and extend quality life years. Screening assays may reduce the incidence of disease and allow effective interventions. Prognostic assays may assist patients and clinicians in making decisions about costly and high-risk interventions.

Background

The National Institutes of Health stated in its 2004 Roadmap for Medical Research that; " *To improve human health, scientific discoveries must be translated into practical application. Such discoveries typically begin at the bench with basic research in which scientists study disease at the molecular or cellular level then progress to the clinical level or patient's bedside* (*The NIH Common Fund*, 2004)." The overarching goal for basic science research at the academic level is to provide clinicians with useful tools to improve patient care and overall human health. The NIH identified three major gaps or roadblocks and sought to: 1) foster high-risk/high-reward research, 2) enable the development of transformative tools and methodologies,

3) fill fundamental knowledge gaps and 4) change academic culture to foster collaboration (*The NIH Common Fund*, 2004).

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention (Strimbu and Tavel, 2010). The academic research environment has invested heavily in biomarker discovery. Mapping of the human genome opened many doors to understanding genomic biomarkers of disease (Pober et al, 2001). A simple PubMed search for "cancer biomarker" generated 181,616 hits. The majority of these publications are discovery data and few focus on translation to a clinically relevant method. Mass spectrometry and array technologies have dramatically increased the number of biomarker discoveries in academia (Anderson, 2005). Large, complex data sets can be generated and analyzed to qualify potential biomarkers of disease (Simon, 2008). Once biomarkers are discovered, a long and tedious path to application in the clinical setting awaits (Figure 1). Resources to execute this path are not clear and many biomarkers never move out of the discovery phase (Phillips et al, 2006). Discovery data are published in peer-reviewed journals and it is left to industry find the most promising prospects for development into useful clinical diagnostic or prognostic assays (Metcalfe, 2010).

Figure 1: Proposed Path From Biomarker Discovery to Clinical Use

The National Institutes of Health have successfully established roadmaps for rapid translation of scientific discoveries at the "bench" to the "bedside" through Clinical and Translational Science Awards (CTSA) focused on interdisciplinary, bidirectional, and collaborative translational research (The NIH Common Fund, 2004). Research centers were developed at universities to dispense CTSA funding to promising researchers concentrating on translational, collaborative projects. The University of North Carolina established the North Carolina Translational and Clinical Sciences Institute (TraCS) to dispense CTSA funds and foster translational research on campus and across the community. Collaboration across universities and between academia and local industry continue to grow through TraCS

connections. Opportunities exist for diagnostic development projects to be funded and well supported through these CTSA awards, yet few biomarker method development projects for clinical laboratory diagnostics are submitted at UNC. When reviewing the awards listed at the TraCS website, around 17% of the awards were biomarker discovery projects but only 0.78% were actual method development projects taking biomarkers to the next milestone in the path. (www.tracs.unc.edu, extracted 9 Mar 11).

Universities are well positioned through the CTSA infrastructure to undertake method development and validation roles in biomarker translation from discovery to clinical use (Zerhouni, 2007). The NIH seeks to fund true translational projects that are able to rapidly bring useful technologies to the clinician to improve patient outcomes. The path for biomarkers requires clear roles for academia, industry and the clinical laboratories in bringing these technologies into practice (Simon, 2008). Barriers exist in all arenas that have delayed development of new clinical diagnostics. By forging a clear path and identifying leadership roles that serve to facilitate biomarker translation from "bench" to "bedside", novel tools will emerge that improve the overall health of patients.

Defining the Role of Academia Along the Path of Biomarker Translation

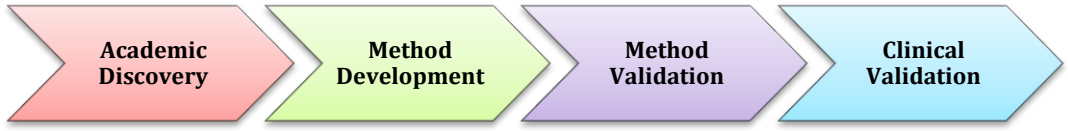
In 2007, a national consortium was launched aimed at transforming how clinical and translational research was conducted in academia (Zerhouni, 2007). Twelve academic health centers were created with funding from CTSAs to push the National Institutes of Health Roadmap for Medical Research initiative (*The NIH Common Fund*, 2004). The overarching goal was to bring treatments efficiently and quickly to patients (Zerhouni, 2007). Today there are fifty-five academic homes for clinical and translational research funded by CTSAs in twenty-eight states (CTSA-NCRR Fact Sheet, 2010). The growth of the CTSAs and focus on translation of technologies and therapeutics from "bench" to "bedside" has created an infrastructure for biomedical research that has never existed (Sampselle et al, 2010).

Focus on working collaboratively, developing career paths, fostering innovation and equipping diverse research teams to translate discoveries into clinical practice is well funded through the CTSAs and provides the infrastructure necessary to move biomarkers down the path from discovery to the point of technology transfer to industry (CTSA-NCRR Fact Sheet, 2010).

CTSA academic homes typically house resources for clinical trial design, regulatory support, biostatistical support, clinical resources, biomedical informatics support and clinical research ethics training (CTSA-NCRR Fact Sheet, 2010). Many of these CTSA academic centers also house biospecimen repositories that further facilitate the ability of academia to translate biomarkers. Access to appropriate specimens for validation has been cited as a major barrier to moving a biomarker to a clinical diagnostic (Phillips et al, 2006).

I propose academia, through the CTSA home, develop a pipeline specifically for biomarker development to include: biomarker discovery, method development, method validation and clinical validation steps on the path towards a clinically relevant diagnostic (Figure 2).

Figure 2 Academia's Role in the Biomarker Development Path



Academic discovery of biomarkers has been thrust forward at lightning speed by the mapping of the human genome and new "omic" technologies (Simon, 2010). Proteomics research has been investigating biomarkers of disease using mass spectrometry techniques to generate large amounts of data and then comparing the entire proteome of diseased versus non-diseased patients using bioinformatics that elucidate the proteins of interest (Cho, 2011). A multitude of papers are published out of academia each year discussing biomarker discoveries for detection of various diseases. However, fewer publications exist at PubMed discussing method development, validation and clinical validation of these newly discovered biomarkers. Studies that exist have very limited sample sizes and are often never developed on a platform that is used in clinical laboratories (Metcalfe, 2010).

Method development beyond the discovery phase must be on a platform readily available to clinical laboratories (Plebani and Marincola, 2006). Discovery methods such as mass spectrometry and genome-wide association analyses are not viable options for clinical laboratories due to cost, time, validation and expertise requirements (Metcalfe, 2010). Academia is well positioned to continue development on clinically relevant platforms that are shared in both research and clinical laboratories. One example is the Luminex© Bead Array technology

that has a global market in both research and clinical applications (Luminex Corp, 2009). Decisions as to which biomarkers show the most promise and justify investment in development and validation should meet the guidelines suggested by Plebani and Marincola (2009):

- The measure should add independent information about the risk or prognosis of disease
- The measure should account for a large proportion of the risk associated with a given disease or condition
- The measure should be reproducible
- To be used as a diagnostic test, the measure should be sensitive and specific and have a high predictive value
- The platform used to develop the marker must be available in both research and clinical laboratories
- Therapeutic modalities should be available showing modification of such a biomarker improves outcomes (i.e. statins and cholesterol levels)

Method validation is vital to successful biomarker translation. Reproducibility of the method across various users and laboratories is required to move on to clinical validation (Plebani and Marincola, 2006). The National Cancer Institutes Early Detection Research Network (EDRN) offers expert collaboration, biorepository access and limited funding for validation studies at the academic level (EDRN 4th Annual Report, 2008). Many universities have resources through the CTSA home to facilitate method validation. Biostatisticians, biorepositories and genomic and proteomic experts along with academic health center clinical laboratory experts are available to collaborate on a development and validation project.

Finally, clinical validation of the biomarker is necessary to prove acceptable predictive values of the measure in the target population. The EDRN along with Dr. Margaret Pepe has set guidelines, forged standardized methods and clinical validation protocols for academia based on industry and government approval requirements for novel diagnostic tests (Pepe, 2010). In addition to the plethora of resources through academic CTSA homes, national resources such as the EDRN also serve to facilitate the successful translation of biomarkers within the academic setting.

Defining Industry's Role Along the Path of Biomarker Translation

Diagnostic test manufacturers such as Roche™, Luminex©, BioRad™ and many others define development and adoption of diagnostics as the "product pipeline" (Phillips et al, 2006). Industry leaders view this product pipeline as starting from biomarker discovery through to a finished FDA-approved diagnostic test ready to be used by clinical laboratories. One of the main reasons for industry to choose not to bring a biomarker to market is poor reimbursement and return on investment (Phillips et al, 2006). The pipeline for biomarker development from discovery to finished product is inherently different than a drug pipeline and results in lower total revenues (Phillips et al, 2006). Clearly there is overlap with the proposed academic roles in discovery and development that may help offset cost to manufacturers.

I propose industry become involved at the technology transfer phase with shared roles in the clinical validation phase (Figure 3).

Figure 3 Industry's Role Along the Path of Biomarker Translation

Clinical validation requires funding that could be shared by academia and industry. Prospective clinical trials are costly. The FDA requires diagnostics to be "*shown safe and effective for their intended use"*(Phillips et al, 2006). Clinical validation in the target population is required to support effectiveness. Diagnostics manufacturers may not have access to patients, biorepositories or epidemiologists to carry out these complex studies. Academic health centers in collaboration with the diagnostics manufacturers would be well equipped to conduct such studies with access to the target population.

Technology transfer (including intellectual property rights) is complicated and a major sticking point of negotiations between academia and industry (Evans and Austin, 2010). With academia generating thousands of potential biomarkers and filing patents on the individual biomarker itself, industry leaders are now required to come to licensing agreements to produce and sell the diagnostic test including such biomarkers (Evans and Austin, 2010). Clearly both academia and industry are highly collaborative in this phase of translation. The academic

Offices of Technology and Development often handle these complex negotiations (Smilor et al, 2007).

The first clear role of industry with minimal collaboration from academia is in the FDA approval phase for the diagnostic. Industry has the resources to compile large pre-market approval packages, 510k applications and CE marking required for diagnostics in the United States and abroad. There are large regulatory affairs departments that handle this phase of the path to a clinically relevant diagnostic. Regular collaboration between government regulatory agencies and industry leaders allows a better understanding of the requirements that must be met to bring a diagnostic to market (Metcalfe, 2010).

The final phases of laboratory adoption and clinical use falls on the marketing departments of diagnostic manufacturers. Once FDA-approval has been obtained, manufacturing and marketing begin. Publications that were submitted to peer-reviewed journals early in the translational path of the biomarker are used to market the assay. Here the earliest phase of biomarker discovery is connected to the final phase of clinical adoption. The importance of proving clinical utility early in biomarker development at the academic level is evident not only to qualify the best candidates for development but use at the later stages of marketing (Bossuyt, 2010).

Barriers and Solutions to Effective and Rapid Translation of Biomarkers

Table 1: Barriers and Solutions to Biomarker Translation

Biomarker Translation Phase	Barrier	Solution
Academic Discovery	• choosing the most suitable biomarker for development investment	• collaboration with clinical laboratories, clinicians and industry leaders and CTSA resources • use 6-criteria from (Plebani and Marincola, 2006)
Method Development	• shortage of experienced personnel to develop biomarkers on commonly used platforms in clinical laboratories • shortage of funding for method development (viewed as R & D)	• provide training through CTSA core facilities on platforms used in clinical laboratories and fund development studies • develop a new core curriculum in method development and validation of clinical laboratory diagnostics • take advantage of clinical laboratory expertise by collaboration with academic health center laboratory directors

	•	•
Biomarker Translation Phase	**Barrier**	**Solution**
Method Validation	• lack of expertise in method validation and expected performance measures for clinical laboratory diagnostics • lack of funding	• EDRN collaboration • NIH Biomarker's Consortium participation • collaboration with clinical laboratory directors
Clinical Validation	• industry access to patients for prospective trials • expertise in study design lacking in industry • access to biorepository missing in industry • lack of clinical knowledge about target population in industry	• academia in collaboration with industry proceed with regulated clinical trials • academia access to CTSA resources for study design and biostatistics support • academia access to biorepositories • collaboration with clinicians in the field of the biomarker's intended use (oncology, cardiology, etc.)
Technology Transfer	• IP rights • reproducibility of method	• Office of Technology and Development at academic institutions get involved early in the process to begin negotiations with industry • collaboration with industry and understanding of FDA expectations for diagnostic assay performance
FDA Approval	• early academic development work may not support submission due to performance in a non-regulated environment	• create biomarker development and validation cores through CTSA homes that adhere to GLP and GCP regulations during method development and validation
Laboratory Adoption	• industry bears the burden of creating a cost-effective, clinically useful, low or moderate complexity diagnostic to gain laboratory adoption	• industry strives for a low-cost manufacturing method • choice of biomarker was valid at the start of the process (high predictive values)
Clinical Use by Providers	• clinicians hesitant to adopt the new technology	• garner the support of clinical experts in the field to promote the diagnostic • perform efficacy studies post-market to show usefulness in the clinical setting

Academic Discovery: Barriers and Solutions

Choosing one or several biomarkers for further development from thousands of potential targets at the discovery phase has proven challenging. Mass spectrometry generates large numbers of potential biomarkers present in diseased patients but absent in healthy controls. Dakna and colleagues (2010) suggests the following questions be asked when choosing a set of biomarkers from a large dataset:

1. Is the frequency or abundance of a certain molecule observed in a proteomic study of disease the result of the disease or artifact due to age, lifestyle, gender, etc?
2. How should the number of samples required for defining the biomarker (s) be estimated?
3. Which algorithms can be employed to combine biomarkers into a multi-marker classifier and how can this algorithm be assessed?

The CTSA home, located across fifty-five academic centers, offers biostatistical support to assist in identification the most clinically relevant biomarkers prior to proceeding to method development and validation phases. A solid training set free of artifact must be identified to avoid failure of biomarker translation later down the path.

Additionally, the six previously discussed criteria are necessary for a forward thinking translational path for biomarkers to make it to the clinical use phase (Plebani and Marincola, 2006). Once a biomarker is chosen, the development of a clinically useful FDA-approved test must be considered when choosing a platform for method development beyond that of the discovery platform.

Method Development: Barriers and Solutions

If design and development of a method is to occur within academia, infrastructure and appropriate curricula must be available. A "method" is the system used to measure the biomarker. Many of the methods used in research laboratories are not used in clinical laboratories (Metcalfe, 2010). Clinical laboratories have high-throughput, automated methods of measuring biomarkers in serum, urine, blood and tissue for single point measurements whereas discovery methods may generate thousands of data points (Metcalfe, 2010). These methods have been validated and meet strict FDA and Clinical Laboratory Standard Institute guidelines. Industry is aware of the needs of the clinical laboratory and has been developing methods appropriate for this environment (their clients).

The CTSA home is the perfect center to add a method development curriculum. With collaborators from industry, academia and often clinical laboratories, the stage is set to turn out

well-prepared researchers specializing in taking newly discovered biomarkers through the method development, method validation and clinical validation phases. Centers of Research Excellence or (COREs) were established at the University of North Carolina's TraCS Institute to assist in developing an idea. One example is the immunology CORE that offers access to instrumentation common in clinical laboratories and collaboration with clinical pathologists. By changing the "discovery" paradigm and moving on to the development and validation phases using platforms and methods already adopted in clinical laboratories, the pipeline is primed for rapid translation of the biomarker down the proposed path.

Many discovery methods are developed routinely in the research setting but few are commonly used in clinical laboratories. It has been suggested that method development curriculum, even at the undergraduate level, be available for scientists in academia as a formal course (Lanigan, 2008). Lanigan suggests method development requires a specialized set of problem-solving skills that include; principles and instrumentation, data analysis, notebook and report writing (2008). All skills are tailored to generate clinically relevant methods and FDA compliant quality documentation that may be utilized anywhere along the path of biomarker translation. Discovery methods are not appropriate for a diagnostic prototype. Curriculum development at the graduate level in the specialized area of clinical method development and validation could rush diagnostics forward while offsetting costs to industry.

Method Validation: Barriers and Solutions

Requirements for method validation in clinical laboratories are standardized and stringent. Academic researchers work in a non-regulated environment and may use any statistical measure they choose to validate the performance of their method. This greatly differs from the clinical laboratory that relies on compliance with the College of American Pathology guidelines and the Clinical Laboratory Standards Institute criteria for method validation (CLSI CAP checklist, 2009). Reproducibility becomes a problem when attempting to transfer the developed method from academia to industry without similar robust performance standards.

The Early Detection Research Network has established validation guidelines, databases and statistical resources to assist academia in moving biomarkers from discovery to clinical use (EDRN 4th Annual Report, 2008). The EDRN also compiles data on the most recent biomarker

discoveries to prevent duplication of efforts and assist industry in keeping current with academic discoveries focused on cancer biomarkers. Collaboration with the EDRN may result in funding opportunities, biorepository access and valuable recommendations when validating a method in the academic setting (EDRN 4th Annual Report, 2008).

Poor analytical performance of biomarkers hinders movement down the path to a clinical application as well as mandating an increased sample size for clinical validation (Zhang and Chan, 2010). The Biomarkers Consortium is a biomedical research partnership between academia and industry that is managed by the Foundations for the National Institutes of Health to move biomarkers toward a useful clinical application (www.biomarkersconsortium.org/about.php, 11 March 2011). The Biomarkers Consortium builds collaborative relationships early in the translational path to facilitate rapid movement from discovery to clinical diagnostic. Ensuring quality analytical performance and qualifying biomarkers for a specific purpose at an early stage is a major focus of the consortium (www.biomarkersconsortium.org/about.php, 11 March 2011).

Collaboration with clinical laboratory directors by basic science researchers through CTSA connections would allow better understanding of the needs of clinical laboratories. This understanding is vital in the early development and validation phases of biomarker translation (Plebani and Marincola, 2006). Most large academic health centers located on university campuses allow for such collaborations and may result in new opportunities for clinical laboratory participation along the method development and validation path.

Clinical Validation: Barriers and Solutions

Method validation proves the test is reproducible and reliable across different users and environments. It seeks to prove the accuracy of the method itself. Clinical validation seeks to prove the biomarker has advantages over other "in use" diagnostics in prediction or prognosis of disease in the target population (EDRN Annual Report, 2008). The ability to discover biomarkers of a biological process is not as challenging as finding biomarkers that differentiate disease versus non-diseased clinical cases. Clinical validation is the most critical step in convincing industry, clinicians and clinical laboratories the biomarker has potential to improve

patient outcomes and to insure reimbursement from payers. Clinical validation requires three phases (EDRN Annual Report, 2008):

1) retrospective longitudinal studies on biobanked specimens from the target population with and without disease to assess preclinical prediction success of the biomarker.
2) Prospective screening of the target population to detect false-positive or false-negative results.
3) Large scale population studies and outcome studies to assess the impact of the biomarker use (cost-reduction, disease burden reduction, disease prevention).

It is challenging for diagnostic manufacturers to gain access to specimens either prospectively or in a biorepository (Phillips et al, 2010). Clinical validation requires appropriately collected retrospective and prospective specimens. More importantly, clinical data on each specimen must be available to appropriately select a cohort for validation. With the Health Insurance Portability and Accountability Act (HIPAA), clinical data is even more difficult to obtain for diagnostic manufacturers. By incorporating sample collection and DNA banking into large campus repositories during all clinical trials, it is possible to consent patients at the time of collection. This allows use of the specimens freely under IRB approval of future studies since HIPPA rights have been waived. Patients have the option to "opt-out" of genetic testing or storage during the consent process. One example of this type of prospective biobanking facilitating the translational process was the discovery of IL28B as a therapeutic response biomarker that predicts clearance of hepatitic C virus (Ge et al, 2009). Without the prospectively collected, multi-center DNA samples that were used for genome-wide association analysis, discovery of IL28B may not have been possible.

Universities with a CTSA home also house large academic health centers where, under IRB approval, clinical specimens and data can be freely accessed for clinical validation purposes. Many CTSAs have begun coordinating large biospecimen repositories on campus with a direct database connection to clinical data to facilitate rapid translation of new technologies (CTSA-NCRR Fact Sheet, 2010). With the coupling of bioinformatics tools, biorepositories and access to patients prospectively, academia is well positioned to take on the clinical validation phase of biomarker translation.

Other limitations in industry may be access to qualified epidemiologists and biostatisticians to design validation studies and lack of access to clinicians treating the target population. It is vital that studies are prospectively designed and sample sizes be appropriately scaled prior to beginning the study.

Additionally, translational science not only wants to move biomarkers from bench to bedside but from bedside to bench. Access to clinicians treating the target population and on-going collaboration is vital to the success of clinical adoption of the final diagnostic product. An understanding of what current guidelines mandate in treatment, diagnosis or prognosis will allow determination of the biomarker's clinical utility. No one understands these guidelines better than practicing clinicians. For example, the American Association for the Study of Liver Diseases recently removed a long standing serum based test, alpha fetoprotein, from the diagnostic algorithm for hepatocellular carcinoma due to low positive and negative predictive values in the at-risk population (AASLD Guidelines, 2010). This major update to the use of this screening test was disseminated at the AASLD annual meeting and rapidly translated into clinical practice. Collaboration with clinicians along the biomarker development path is vital to keeping abreast of clinical practices and adhering to the NIH's translational science mandate.

The cost of clinical validation is a major barrier to moving promising, well-qualified biomarkers forward (Phillips et al, 2006). Diagnostics are viewed by industry as less profitable than drugs and a high-risk endeavor (Metcalfe, 2010). If the resources at the large academic institutions are utilized during clinical validation cost can be minimized. The CTSA home is a one-stop source of resources to carry out these studies. Joint funding from industry partners, CTSAs and government could minimize the financial impact to one collaborator.

Technology Transfer: Barriers and Solutions

In recent years, industry has come to rely heavily on academia for new biomarker discoveries (Patino, 2010). The focus of diagnostic manufacturers is not discovery but development and marketing. This collaborative relationship between academia and industry has become complicated with intellectual property and licensing slowing the translational process.

A breakout session at the 2010 CTSA Industry Forum focused on medical device translation and technology transfer identified the following challenges facing progression from an academic discovery to clinical diagnostic (Linehan and Chaney, 2010):

1) incomplete understanding by faculty of the medical device commercialization landscape
2) inadequate funding for proof of concept projects
3) limited understanding of regulatory science
4) lack of active project management of development/validation projects in academia
5) inconsistent and perceived non-collaborative university intellectual property policies
6) poor communication between stakeholders
7) fragmented medical device markets that are smaller than those for drugs that require business development skills and market expertise not readily available in academia
8) disciplinary knowledge silos-virtual academic environments that act as barriers to intellectual collaboration.

Offices of Technology and Development (OTD) have sprung up across college campuses to address these issues. Similar to the CTSA homes, OTDs serve to collaborate at the earliest stages with academic inventors and industry leaders to secure patents and later negotiate IP rights and licensure. Many CTSA homes have created a commercialization core to work closely with researchers and OTDs to secure IP and transfer the technology to industry.

There are many options in partnering with industry early in the path for technology transfer. If the diagnostic will require high-cost testing and validation to prove its utility, partnering early with an industry partner can help in offsetting some of the initial costs (clinical validation phase) (Patino, 2010) and allow industry to assist in informing academic researcher of the FDA guidelines for biomarker validation (Scherf et al, 2010). Of course, lower royalties will result in early investment in academic development but may allow the biomarker to make it out of the discovery and method validation phase.

One option for successful technology transfer of a diagnostic is to partner with pharmaceutical companies in clinical trials where the biomarker may offer useful data for drug development. The co-development of the biomarker with the drug is fast gaining popularity in industry as companion diagnostics continue to grow. One success story was the development of the breast cancer drug Herceptin and the companion diagnostic genetic test Her2/*neu* (Ross, 2003). The drug is given to patients with a breast cancer expressing Her2/*neu* protein. The diagnostic test followed a parallel path with drug development from the clinical trial stage to release of Herceptin with the mandatory genetic test written into the package insert (Ross, 2003).

The overarching goal is to find a path that will speed negotiations in transferring the technology from academia to industry partners for use in the clinical setting. By following the proposed path for biomarker development, whereby academia hands off the technology at the tech transfer phase with some overlap in clinical validation, delays at the tech transfer phase may be avoided. Starting IP negotiations at the method validation phase, once a valid discovery set of data has been found and prior to publishing, will also speed the translation process (Patino, 2010).

FDA Approval: Barriers and Solutions

By the time a biomarker is facing FDA approval, the technology has been transferred to industry and preparation of either a premarket approval or 510k applications can begin. Premarket approvals are required for any diagnostic test that poses higher risk to the patient as defined by the FDA (FDA 21 USC 360c (a)(1)). A 510k can be submitted if a predicate diagnostic exists and the new technology poses a low-risk to the patient. Either of these applications places the burden of proving the diagnostic supports its intended use claim and is a reliable method. The FDA also classifies biomarkers into the following categories (Scherf et al, 2010):

1) Diagnosis: provide information about a disease or condition typically used in the at-risk population.
2) Early Detection (screening): used for early detection of disease in the general population. Prevalence of the disease in the general population will determine performance of the biomarker.

3) Monitoring: used for follow-up of a previously diagnosed disease or condition. May be used in conjunction with other monitoring technologies.
4) Prognostic: predicts the outcome of a previously diagnosed disease independent of a specific treatment. Assessed in time to event or survival time.
5) Safety: predicts the risk of an adverse event usually associated with a treatment with a drug or other technology.

Barriers that exist for FDA approval of a biomarker are many. Data generated along the proposed pipeline in academia from discovery to clinical validation may not be valid for use in the FDA application due to the regulatory compliance adhered to during collection (Pirmohamed, 2010). If data are collected under Good Clinical Practices Guidelines or Good Laboratory Practice guidelines as proposed by the FDA, data are sufficient to be included in the application. There is limited information regarding effective means of shared development between academia and industry that supports FDA regulatory requirements for approval (Scherf et al, 2010). The path proposed in this paper is one suggested co-development strategy.

I propose, through CTSA homes, that academia form a new center of excellence specifically devoted to biomarker method development, method validation and clinical validation phases. After discovery of a biomarker, the data could be transferred to the project management and scientific development team within a fully GLP compliant laboratory on campus. By assigning a project management team and having experts in the area of clinical laboratory method development and validation, the data generated under these regulatory guidelines are capable of being included in the FDA approval package. This mitigates cost to industry and creates incentive for industry to invest in a well-qualified biomarker (Pirmohamed, 2010). The development and validation laboratory may generate revenue for the university if costs are associated with the service and potential outside funding by both government and industry are obtained. A core laboratory shared between collaborating universities may be an option to propel biomarker development forward and generate more well qualified biomarkers that appeal to industry investors yet mitigate costs to the individual universities.

Laboratory and Clinical Adoption: Barriers and Solutions

If the method chosen for development of the promising biomarker was well planned to cater to the needs of the clinical laboratory and the biomarker has been successfully proven to be cost-effective and efficacious, adoption into use across clinical laboratories will be easy. Clinicians are looking for a new tool to have in their bag that will give them new or promising information to improve outcomes for patients. Providing evidence of the biomarkers clinical validity is required to change existing practices (Pirmohamed, 2010). Although clinical utility may be the first question asked by clinical laboratories considering a new diagnostic, reimbursement questions will soon follow. Even when a new diagnostic test has clinical utility, if it is not reimbursable, adoption may not be considered.

Proving clinical validity and usefulness of a biomarker as well as ensuring reimbursement can be easily addressed by making an upfront investment in cost-effectiveness and cost-utility studies during the clinical validation phase (Scott, 2010). Scott suggests the following types of studies to overcome barriers of laboratory and clinical adoption of novel biomarkers (2010):

1) **Cost minimization analysis**: simple economic analysis that looks at two or more tests that produce the same outcome to determine which is the least expensive. Measures such as cost per test may be used.
2) **Cost-effectiveness analysis**: evaluate the most efficient way of using limited and fixed resources that achieve the greatest positive effect on patient outcomes. Measures such as quality life years may be used.
3) **Cost-benefit analysis**: costs of the benefit are compared to cost of the test. Measures that compare life years with cost may be used.
4) **Cost-utility analysis**: estimates the ratio between the cost of the test and the number of years gained in good health. Measures are in monetary units and may include quality adjusted life years (QALYs).

A theoretical example given by Scott (2010) of a biomarker cost-utility analysis is as follows:

- **Biomarker Intended Use**: Detection of esophageal adenocarcinoma (EAC) in high-risk population having Barrett's esophagitis.

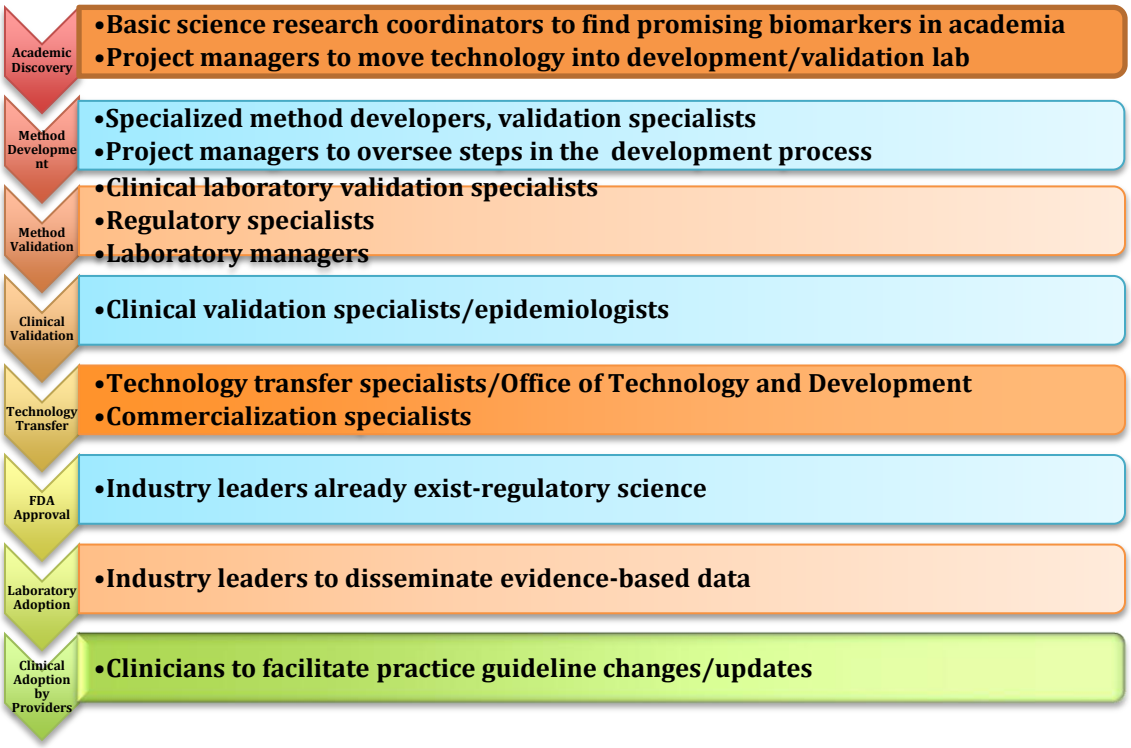
- **Incidence of EAC in the U.S. annually**: 6,500 persons
- **Risk factors**: gastroesophageal reflux (GERD) increases of EAC and Barrett's esophagitis (BE) increases risk by 40-fold
- **Current screening practice**: perform endoscopy in patients with GERD and if BE is present, repeat every three years thereafter or more frequently if dysplasia is found
- **Calculation**: Fixed costs for endoscopy, espophagectomy, postsurgical care, cancer care and clinic visits were incorporated into a Markov model.
- **Conclusion**: an EAC biomarker with 80% sensitivity and 95% specificity for EAC would be cost effective with an incremental cost-effective ratio (ICER) of less than USD 50,000 per QALY. At a biomarker cost of USD 1,000, the sensitivity and specificity would need to be 90% and 97% to meet the USD 50,000 per QALY threshold.

Publications with this type of analysis are few but will increase as payers demand evidence that a biomarker will reduce the overall cost of care and clinicians demand new decision support tools to improve health outcomes for their patients (Pirmohamed, 2010). These types of analyses could be done theoretically before the clinical validation data are complete or retrospectively using these data. The bottom line is that these types of studies are going to be necessary for both currently used clinical laboratory tests and new tests prior to investment. Sensitivity and specificity targets could be set before the assay moves into the method development phase to insure cost-effectiveness of the final product.

Leadership Positions Necessary to Support the Proposed Path

Many new leadership positions will be necessary to keep the proposed biomarker development path moving forward efficiently (Figure 4).

Figure 4: Leadership positions along the path



As the field of translational science continues to grow and collaborative research becomes the norm across academia, industry and government, opportunities will become evident not only for biomarker translation but for any therapy or technology. Career development is a primary initiative of the CTSA homes and as such would be the ideal entity to develop the proposed translational path for biomarkers and train individuals to fulfill these positions.

Implications of Rapid Biomarker Translation to Public Health

Laboratory diagnostics that are delivered for clinical use must be both efficacious and effective. Efficacious biomarkers perform well in a controlled environment and show high values for precision and accuracy. Effective biomarkers perform well in the real world; the target population. Biomarkers must have high predictive values to be effective and be a useful tool in the hands of clinicians.

Screening biomarkers, such as the OraSure™ HIV Rapid Oral screening test have revolutionized HIV detection in the general population. Outreach non-profit organizations, open-door clinics and other organizations have utilized this easy to use diagnostic device that

requires a swab of the mouth and 2 minutes to get a result. Trained professionals have been able to go into venues where high-risk populations are not reached by traditional health providers and screen for disease, discuss prevention and refer for care early in the disease course. The overall incidence of disease may be decreased due to these combined screening and prevention efforts.

As healthcare costs continue to rise due to the introduction of more costly technologies, it is imperative clinicians have tools to make informed decisions about the best and most effective therapies. Predictive or prognostic biomarkers may provide information to make informed decisions about future screening frequencies, high-risk treatment regimens and follow-up procedures. If a diagnostic exists that could predict risk of developing cancer in a high-risk population, those in the high-risk group could have more frequent screening while those in the low-risk group could reduce follow-up visits. Accurate prognostic assays may provide enormous cost savings to an already stressed healthcare system.

Conclusion: A Biomarker Success Story

The OVA1 diagnostic test for ovarian cancer is the first assay to be FDA cleared as an In Vitro Diagnostic Multivariate Index Assay (IVDMIA) (Zhang & Chan, 2010). The OVA1 algorithm uses results from five separate protein biomarkers of ovarian cancer. Results are combined to yield an index score between 0-10 that classifies women with an adnexal mass into high or low risk groups for ovarian cancer (Zhang and Chan, 2010). The assay began in the academic setting with proteomic discovery of many biomarkers of ovarian cancer with appropriate methods used to choose the best five combinatorial grouping.

Zhang and Chan (2010) suggest three key bridges in the biomarker development path that were keys to the success of their assay:

1) generate sufficient and "portable" evidence in early validation studies to support investment for large-scale validation studies.
2) Define clinical utility that balances desire for broad applicability and feasibility for completing clinical trials for regulatory approval.
3) Select and develop assays with analytical performance suitable for clinical deployment.

For OVA1 the clinical utility of the test was to determine ovarian cancer risk in women presenting with an adnexal ovarian mass. The clinical validation set out to prove this single claim. Serum samples from multiple academic health centers were obtained to not only increase sample size but also reduce bias during a prospective clinical trial. In the early stages of discovery, over 500 retrospective samples were assessed and a mass spectrometry method employed to analyze these samples. It was soon evident that this mass spectrometry method would not be suitable for a clinical assay due to poor analytical performance (Zhang and Chan, 2010).

A suitable multiplex method was not used in the OVA1 case. The Luminex™ multiplex platform would have been one option. However, the developers of the assay decided to develop a mathematical model that combined previously approved individual diagnostic assays to generate the risk score. The FDA actually gave approval to the algorithm just as it would have a newly developed method (Zhang and Chan, 2010). This opened the door to new data mining and machine-learning algorithms that combine currently used clinical diagnostics to improve the sensitivity and specificity of single markers such as CA125 for ovarian cancer.

After Quest Diagnostics, a large reference laboratory licensed the FDA cleared algorithm and began marketing the assay, clinicians were reluctant to adopt the new assay (Muller, 2010). It was suggested that caution be used when using the OVA1 test and it should never be used alone for making clinical decisions (Muller, 2010). The clinical validation study had not been published for the trial but the results of the trial had been disseminated to clinicians as well as consumers. In my opinion, an error occurred here in the translational pathway. The clinical validation and cost-effectiveness studies should have been published first with dissemination to clinicians first at annual meetings. Once adopted by clinicians, they would have been the best source for consumer information and a healthy trust would have been established between Quest Diagnostics and providers.

The future is bright for biomarker translation from discovery to clinical adoption. Zhang and Chan (2010) suggest several bridges to smooth the path. Their suggestions support the proposed path in this paper. Although a mistake was made at the end of the path in dissemination of the data to the appropriate stakeholders, approval of OVA1 laid the groundwork for a successful model from discovery to clinical adoption.

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